The emerging role of PD-1/PD-L1 inhibitors in unresectable locally advanced esophageal squamous cell carcinoma: current status and challenges

Hui Yang, Hong Ge*

Department of Radiation Oncology, the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, 450052, China

Submitted: 30-Jun-2022

Sent for review: 11-Jan-2023

Accepted: 12-Mar-2023

Reviewed by Fuyou Zhou

*Corresponding author: Hong Ge
E-mail: gehong616@126.com

Abstract

Esophageal squamous cell carcinoma (ESCC) is one of the most common cancers with high mortality in China. For unresectable locally advanced esophageal squamous cell carcinoma (LA-ESCC) patients, concurrent chemoradiotherapy (CRT) remains as a standard treatment. With the rapid development of anti-programmed death 1/ anti-programmed death ligand 1 (PD-1/PD-L1) inhibitors, more and more combinations of PD-1/PD-L1 inhibitors and CRT were studied in clinical trials of unresectable LA-ESCC. In this review, we conclude the different combination sequences of clinical trials as sequential, induction, and concurrent models. Only two published with concurrent PD-1 inhibitor and CRT demonstrating the endurable toxicities and promising efficacy. Further results of ongoing studies may indicate the best combination sequencing in treatment of LA-ESCC. On the other hand, we focus on the predictive factors for combined modality therapy. Thus far, the roles of PD-L1 expression and tumor mutation burden (TMB) are controversial. Moreover, the predictive potential of tumor microenvironment (TME), genetic, dynamic blood and non-invasive radiomic biomarkers for ESCC prognosis were also discussed, indicating combined prediction models with multiple dynamic biomarkers may be available in the future.

Keywords: Locally advanced esophageal carcinoma, Chemoradiotherapy, Immunotherapy, Combination therapy

Introduction

Esophageal cancer (EC) is the seventh most common cancer and ranks sixth in the cause of cancer-related death worldwide [1,2]. Among 60,100 new cases in 2020, 53.7% of them occurred in China [2]. Esophageal squamous cell carcinoma (ESCC) is the predominant histological type in China and is closely associated with smoking, having hot food or water, and alcohol consumption [3].

As of now, more than 70% of patients are unresectable locally advanced ESCC (LA-ESCC) or metastatic ESCC when diagnosed. Unresectable LA-ESCC has been defined as T4b disease, N3 disease with multisite or bulky lymph nodes or non-regional lymph nodes metastases according National Comprehensive Cancer Network (NCCN) guideline[4]. Currently, the standard therapy for unresectable LA-ESCC patients is still definitive concurrent chemoradiotherapy (CRT) based on the results of the clinical trial RTOG 85-01[5]. However, 40-60% of unresectable LA-ESCC patients relapse quickly after CRT and the five-year survival rate is only 21-28%[5-7].

Researchers have continuously attempted to prolong the long-term survival time and improve the local control rate of unresectable LA-ESCC patients. Unfortunately, neither high-dose radiotherapy[8] nor chemotherapy improvement[9] could lengthen the survival of patients. In recent clinical trials of ESCC, immunotherapy, especially anti-programmed death 1/anti-programmed death ligand 1 (PD-1/PD-L1) inhibitors, is expected to induce more clinical benefit in metastatic or recurrent ESCC patients. The results of KEYNOTE-181 (NCT02564263), Attraction-3 (NCT025569242), ESCORT (NCT03099382), ORIENT-2 (NCT03116152), and RATIONALE-302 (NCT03430843) support various PD-1/PD-L1 inhibitors as second-line treatment in metastatic or recurrent ESCC patients [10-15]. The clinical trial KEYNOTE-590 (NCT03189719), CheckMate 648 (NCT03143153), ESCORT-1st (NCT03691090), and ORIENT-15 (NCT03748134) further promote the first-line usage of PD-1/PD-L1 inhibitors in advanced ESCC patients [10,16-19]. Based on the large-scale, randomized controlled trial (RCT) KEYNOTE-181, pembrolizumab was approved as a second-line treatment in advanced ESCC with PD-L1 combined positive score (CPS) ≥10[15]. Moreover, the combination of pembrolizumab and traditional chemotherapy was recommended as first-line treatment in advanced ESCC based on the KEYNOTE-590 study [16]. These promising advances have caught more interest in the role of PD-1/PD-L1 inhibitors in unresectable LA-ESCC patients. In this review, we focus on the synergistic effect of immunotherapy and CRT, summarize the ongoing clinical trials of trimodality therapy as first-line treatment, and conclude the potential predictive factors in LA-ESCC.

Synergistic effect of immunotherapy and chemoradiotherapy

Various immunotherapies act on different steps of anti-tumor immunity to enhance the host's immunity and strengthen anti-tumor immune responses. The cancer-immunity cycle consists of tumor-specific antigens recognition, antigen presentation, T cell activation, infiltration to cancer cells, and cancer cell killing [20]. The PD-L1 on the surface of tumor cells binds to the PD-1 on immune cells, weaken cytotoxic T lymphocyte, inhibit T cells, and eventually leading to immune escape in tumor microenvironment [21]. Hence, PD-1/PD-L1 inhibitors block the binding of PD-1 and PD-L1 and serve in the effector phase of the cancer-immunity cycle.

Radiotherapy causes random point mutations and double-stranded breaks in the DNA, increasing tumor mutation burden (TMB) and neoantigens. Radiation-induced cell death is a kind of immunogenic cell death (ICD) as it promotes tumor antigen progression and presentation, dendritic cells activation and

maturation, and cancer cells recognition and elimination by T-cells and NK cells[22,23]. On the other hand, radiotherapy can modify the immunosuppressive tumor microenvironment (TME). Specifically, radiotherapy increases the expression of vascular adhesion molecule-1 (VCAM-1) on endothelial cells, permits the extravasation of T-cells[24], and reprograms macrophages to secrete nitric oxide (NO) which enhances T-cell infiltration and vascular normalization[25]. In addition, radiotherapy was reported to increase the expression of PD-L1 on cancer cells [26]. Preclinical studies indicated increased PD-L1 expression in irradiated tumors and provided evidence for the synergetic effect of combining PD-1 inhibitors and radiation in LA-ESCC[27]. Hence, combining PD-1/PD-L1 inhibitors and radiotherapy could strengthen antitumor immunity in the TME[28].

The combination of chemotherapy and PD-1/PD-L1 inhibitors is common in diverse cancer diseases. Chemotherapy causes ICD and promotes antiangiogenesis [29]. Also, it enhances the maturation of dendritic cells and proliferation of effector T cells and selectively depletes immunosuppressive cells in the TME[29].

Radiotherapy and chemotherapy could convert non-immunogenic tumors into immunogenic ones and produce synergetic effects. Therefore, it is reasonable to combine CRT with PD-1/PD-L1 inhibitors in unresectable LA-ESCC.

Current studies of combined modality therapy

After searching the ClinicalTrials.gov database, we summarized the trials of unresectable LA-ESCC with combined PD-1/PD-L1 inhibitors and CRT in Table 1. The combined modality therapies are mainly three models: 1. Sequential therapy: patients receiving PD-1/PD-L1 inhibitors after CRT; 2. Induction therapy: patients receiving CRT after PD-1/PD-L1 inhibitors; 3. Concurrent therapy: patients receiving CRT and PD-1/PD-L1 inhibitors concurrently. So far, most studies are still ongoing and the results yet to be published. Only two studies (NCT03671265 and NCT04005170) with concurrent therapy were available.

Table 1. Current studies of combined modality therapy

Clinical trial	Phase	Study design	PD-1/PD-L1 inhibitor	Chemotherapy	Radiotherapy	Sequencing
UMIN000034373 (TENERGY)	II	Single-arm	Atezolizumab	CF	60.0Gy/30F	Sequential therapy
NCT04543617 (SKYSCRAPER-07)	III	RCT	Atezolizumab (+ Tiragolumab)	NM	NM	
NCT03817658	II	RCT	Camrelizumab	CF	45.0-50.0Gy/25F	Induction therapy
NCT04054518	II	Single-arm	Durvalumab	NM	NM	
NCT03985046 /NCT04212598 /NCT04514835						Concurrent therapy
NCT03278626	I/II	Single-arm	Nivolumab	TP	50.4Gy/28F	

Table 1. (continued)

Clinical trial	Phase	Study design	PD-1/PD-L1 inhibitor	Chemo-therapy	Radiotherapy	Sequencing
NCT04084158	II	RCT	Toripalimab	TP	PTV 50.4Gy/28F; PGTV 61.6Gy/28F	
NCT04844385	II	Single-arm	Toripalimab	TP	60.0Gy/24F	
NCT03671265	I	Single-arm	Camrelizumab	DP	60.0Gy/30F	
NCT04426955	III	RCT	Camrelizumab	TP	50.4Gy/28F	
NCT04550260	III	RCT	Durvalumab	CF	50.0-64.0Gy	
NCT04210115	III	RCT	Pembrolizumab	CF/ FOLFOX	60.0Gy/30F	
(KEYNOTE-975)					50.0Gy/25F	
NCT04602013	II	Single-arm	Sintilimab	TP	60.0-66.0Gy/30-33F	
NCT03957590(RATIONALE 311)	III	RCT	Tislelizumab	TP	50.4Gy/28F	
NCT04005170	II	Single-arm	Toripalimab	TP	50.4Gy/28F	

Abbreviations: CF: fluorouracil and cisplatin/carboplatin; DP: docetaxel and cisplatin/carboplatin; FOLFOX: fluorouracil + oxaliplatin + leucovorin or levoleucovorin; NM: not mentioned; TP: paclitaxel and cisplatin/carboplatin.

NCT03671265

Phase Ib, single-arm study NCT03671265 investigated the safety and feasibility of combining concurrent CRT with camrelizumab as first-line treatment for unresectable LA-ESCC patients[30]. Patients received concurrent CRT and PD-1 inhibitor (docetaxel 25mg/m^2/w plus cisplatin 25mg/m^2/w for 4 weeks; 60 Gy/30 fractions; and camrelizumab 200 mg/2w for 32 weeks). In the twenty enrolled patients, grade 3 adverse events (AEs) occurred in nine (45%) patients, and no grade 4 or 5 AEs were observed. The most common grade 3 treatment-related adverse events (TRAEs) were radiation esophagitis (four (20%) patients), and others included esophageal fistula, pain, and decreased white blood cell count (each in two (10%) patients). Serious TRAEs occurred in eight (40.0%) patients, including radiation esophagitis (four (20%) patients), and esophageal fistula, radiation pneumonitis, and pulmonary infection (each in two (10%) patients). Immune-related adverse events (IRAEs) occurred in eleven (55%) patients. Of note, the most common IRAEs were grade 1 reactive capillary endothelial proliferation (RCCEP) (ten (50%) patients) and grade 1 hypothyroidism (three (15%) patients). No treatment-related deaths.

Thirteen (65.0%) patients had an objective response (ORR) after the radiation of 40 Gy, including two (10%) complete responses (CR) and eleven (55%) partial responses (PR). The median time to recurrence was 8.25 months (range: 4.68-11.82 months). Tumor recurrence occurred in six (30%) patients, including one (5%) local regional failure, three (15%) cases of distant metastasis, and two (10%) with concurrent regional failure and distant metastasis. The progression-free survival (PFS) time ranged from 4.9 to 28.5 months, and overall survival time (OS) varied

from 8.2 months to 28.5 months (median OS and PFS not reached). The 1-year and 2-year OS rates were 85.0% and 69.6%, respectively. The 12-month and 24-month PFS rates were 80.0% and 65.0%, respectively.

NCT04005170

Another phase II, single-arm study NCT04005170 enrolled untreated, unresectable, stage II-IVA ESCC patients. Patients also received concurrent CRT and PD-1 inhibitor (paclitaxel 50 mg/m^2/w and cisplatin 25 mg/m^2/w for 5 cycles; 50.4 Gy/28 fractions; and toripalimab 240 mg/3w for 12 months or disease progression)[31]. Forty-two patients (two stage II, nineteen stage III, and twenty-one stage IVA) were enrolled and thirty-nine of them received completed CRT treatment. Twenty-eight patients were suitable for efficacy analysis and all patients were for safety analysis. Twenty patients (47.6%) experienced grade ≥3 AEs and one patient (2.4%) suffered grade 5 esophageal fistula. The most common grade ≥3 AEs were lymphopenia (45.2%), neutropenia (33.3%), and anemia (28.6%), respectively. The CR rate was 60.7% (17/28), and the median OS and PFS were not reached.

Hence, the concurrent addition of PD-1 inhibitors to definitive CRT as first-line treatment for LA-ESCC demonstrated acceptable toxicity and promising anti-tumor efficacy.

NCT03278626 and NCT04084158

We also noticed two stopped trials. The phase I/II, single-arm study NCT03278626 enrolled untreated N1-3 or T3-4 N0 ESCC patients[32]. It was terminated earlier than anticipated due to slow accrual and was revealed on March 28, 2022. Seven of the twelve enrolled patients finished combination therapy. In the induction phase, patients received two cycles of nivolumab (240 mg/2w) alone. After that, patients received concurrent CRT (paclitaxel 50 mg/m^2/w, carboplatin AUC=2/w; 50.4 Gy/28 fractions) and nivolumab (240 mg/2w for 6 weeks). Of them, two (16.7%) patients died, and one patient withdrew because of toxicity. The other one patient did not complete due to the disease progressed. Six (50.0%) patients had serious TRAEs, including myocardial infarction, abdominal pain, colitis, dysphagia, esophagitis, fever, lung infection, confusion, aspiration, and rash-morbilliform (each in one (8.3%) patient). The AEs happened in more than 50% patients were anemia (91.7%), decreased platelet count (75.0%), decreased white blood cell count (75.0%), dysphagia (66.7%), hypokalemia (58.3%), and nausea (58.3%).

The other suspended study NCT04084158 had a similar design. It is a randomized, phase II study and aimed to compare standard concurrent CRT and trimodality therapy in LA-ESCC patients[33]. The combination therapy includes the induction phase (toripalimab 3mg/kg/2w for two cycles), concurrent CRT and PD-1inhibitor, and maintenance phase (toripalimab 3mg/kg/2w for up to one year). Researchers suspended this study because of the significantly poor prognosis in the combination arm. No detailed data was available thus far.

Considering the poor prognosis and toxicities in the two trials, the design of induction immunotherapy may not be a good choice for unresectable LA-ESCC patients. Clinical trials with different designs are ongoing now. Further study results may help to identify proper combination models.

Predictive factors for beneficial patients

Various predictive biomarkers are studied to identify patients who are most likely to benefit from PD-1/PD-L1 inhibitors in ESCC. We conclude different biomarkers, including PD-L1, TMB, TME biomarkers, genetic biomarkers, dynamic blood biomarkers and non-invasive radiomic biomarkers.

PD-L1 status

The correlation between expression of PD-L1 and efficacy of PD-1/PD-L1 inhibitors in ESCC remains unclear. The KEYNOTE-180 trial and KEYNOTE-181 trial reported that only PD-L1 positive (CPS ≥ 10) ESCC patients could benefit from single-agent pembrolizumab treatment[15,34]. ORIENT-2

study also found only PD-L1 positive patients could benefit from sintilimab compared with chemotherapy [13]. However, all patients had a benefit in overall survival regardless of PD-L1 expression in the trials of Attraction-3, ESCORT, and RATIONALE-302 [11,12,14].

Furthermore, PD-L1 status may not be a predictive factor when combined with chemotherapy or CRT in ESCC[18,19]. The trial NCT03671265 about camrelizumab showed that high baseline tumoral PD-L1 expression (cutoff value: 7.613%) is not associated with longer OS in LA-ESCC patients when combined with CRT ($P = 0.055$)[30].

TMB

TMB is the number of non-synonymous somatic gene mutations (Mb) of sequenced DNA, and higher TMB is associated with enhanced anti-tumor immunity.

In the phase Ib/II trial, NCT02915432, chemo-refractory ESSC patients received toripalimab and performed whole-exome sequencing (WES), messenger RNA sequencing, and immunohistochemistry (IHC) on the samples. Eleven (23.4%) patients with high TMB (≥12 Mutations/Mb) showed no significant advantage in ORR or OS[35]. Besides, the biomarker analyses from ORIENT-02 reported a median TMB of 6 Mutations/Mb (ranging from 1 to 29 Mutations/Mb). No association between TMB and survival was observed in the study[30], which warrants more studies to evaluate the role of TMB and its proper cutoff value in ESCC patients.

TME

The efficacy of cancer therapies was highly affected by the immune cell frequency in the TME, including dendritic cells, macrophages, tumor infiltration lymphocytes (TILs), and so on. Therefore, their role in LA-ESCC needs to be investigated.

The trial NCT02742935 found that high baseline levels of tumor $CD11^+$ dendritic cells are related to the improved OS in ESCC patients with combination therapy[30]. The immune cell infiltration analysis from The Cancer Genome Atlas (TCGA) and the immunology database and analysis portal (ImmPort) database showed that the high level of B cell infiltration is correlated with a poor prognosis of ESCC ($P < 0.05$) [36]. The other six kinds of immune cell infiltration (CD4-T cell, CD8-T cell, macrophage, neutrophil, and dendritic cell) have no statistical correlation with prognosis.

Genetic biomarkers

Despite the biomarkers mentioned above, many genetic biomarkers are investigated now. The trial NCT02915432 about toripalimab evaluated genomic and transcriptional biomarkers. The copy number analysis identified that 48% (24/50) patients have 11q13 amplification, which resulted in elevated mRNA expression of corresponding genes, including Cyclin D1 (CCND1) and fibroblast growth factor family members (FGF3/4/19)[35]. Moreover, patients without 11q13 amplification have considerably better ORR (30.8 vs. 4.2%, $P = 0.024$) and PFS (3.7 vs. 2.0 months; harzard ratio (HR) = 0.47, 95% confidence interval (CI): 0.24-0.91, $P = 0.025$). The trial NCT03671265 of camrezulimab also revealed that patients with amplification of CCND1, FGF19, or FGF4, have significantly different OS compared with those with normal expression[30].

Based on TCGA and ImmPort data sets, researchers identified some immune-related genes (BMP1, EGFR, S100A12, HLA-B, TNFSF18, IL1B, MAPT, and OXTR) that were associated with the clinical prognosis of ESCC. The survival of the patients with high immune-related genes scores was significantly lower than that of patients with low scores ($P < 0.001$) [36].

Dynamic blood biomarkers

In the trial NCT02742935 about camrelizumab, ESCC patients with an increased baseline lactate dehydrogenase (LDH) had lower ORR ($P = 0.02$) and shorter PFS ($P = 0.002$) and OS ($P < 0.0001$) than patients with normal LDH[37]. Meanwhile, the increase of LDH during the treatment (HR = 0.18), C-reactive protein (CRP) (HR = 0.27), and absolute monocyte count (HR = 0.33) were independent prognostic fac-

tors. ORIENT-2 study also reported that patients with neutrophil to lymphocyte ratio (NLR) < 3 at six weeks post-treatment have a significantly prolonged median OS (16.6 months) compared with NLR ≥ 3 [13].

The trial NCT02742935 also evaluated the levels of immune-related cytokines in baseline and on-treatment peripheral blood. Both baseline and on-treatment IL-27, and high baseline IL-15 were associated with better OS[30]. While a high baseline Eotaxin-3 and a high on-treatment IL-22 were correlated with worse OS[30], the other cytokines were not related to survival.

Radiomic biomarkers

With the rapid development of artificial intelligence (AI) in medical imaging, radiographic characteristics of tumors referred to as 'radiomics' have been used to predict prognosis in different tumors. The study enrolled sixty-four advanced, unresectable ESCC patients treated with sintilimab (200 mg/3w) plus chemotherapy (docetaxel 60 mg/m^2/3w and carboplatin AUC=5/3w) at two centers[38]. A total of 788 features were extracted and radiomics models were built on corrected/uncorrected 2D and 3D features by using 5-fold cross-validation. The 2D corrected radiomics model yielded the optimal performance in this study and could facilitate noninvasive preselection of ESCC patients who would benefit from the combination therapy.

Currently, due to the predictive power of a single biomarker being limited, combined prediction models with multiple biomarkers would be necessary to predict the prognosis of cancer patients.

Prospect

Despite the PD-1/PD-L1 inhibitors are widely evaluated in unresectable LA-ESCC patients now, the proper combination therapies of CRT and PD-1/PD-L1 inhibitors to produce satisfactory efficacy and acceptable toxicity remain to be certified. The current published results of the clinical trials suggest that concurrent therapy with CRT and PD-1/PD-L1 inhibitors could be a good choice. Further results are required to recommend the durable and promising combination sequence for LA-ESCC. Future studies with more clinical trial evidence may dramatically change the current treatment for LA-ESCC patients and aid to identify patients who most likely gain clinical benefits from PD-1/PD-L1 inhibitors. Additionally, future studies including specific predictive biomarkers for LA-ESCC with trimodality therapy, dynamic blood indices, and non-invasive radiomic biomarkers are all warranted to establish an optimum combined therapeutic regimen and a more accurate prediction model for LA-ESCC.

Conflict of Interest

The authors have no conflicts of interest to disclose.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; 70:7-30.

[2] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209-49.

[3] Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013; 19: 5598-606.

[4] Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN Clinical Practice Guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 855-83.

[5] Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; 281: 1623-7.

[6] van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal

or junctional cancer. *N Engl J Med* 2012; 366: 2074-84.

[7] Versteijne E, van Laarhoven HW, van Hooft JE, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. *Dis Esophagus* 2015; 28: 453-9.

[8] Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; 20: 1167-74.

[9] Chen Y, Ye J, Zhu Z, et al. Comparing paclitaxel plus fluorouracil versus cisplatin plus fluorouracil in chemoradiotherapy for locally advanced esophageal squamous cell cancer: a randomized, multicenter, phase III clinical trial. *J Clin Oncol* 2019; 37: 1695-703.

[10] Yang H, Wang K, Wang T, et al. The combination options and predictive biomarkers of PD-1/PD-L1 inhibitors in esophageal cancer. *Front Oncol* 2020; 10: 300.

[11] Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; 20: 1506-17.

[12] Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* 2020; 21: 832-42.

[13] Xu J, Li Y, Fan Q, et al. Clinical and biomarker analyses of sintilimab versus chemotherapy as second-line therapy for advanced or metastatic esophageal squamous cell carcinoma: a randomized, open-label phase 2 study (ORIENT-2). *Nat Commun* 2022; 13: 857.

[14] Shen L, Kato K, Kim SB, et al. Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma (RATIONALE-302): a randomized phase III study. *J Clin Oncol* 2022: JCO2101926.

[15] Kojima T, Shah MA, Muro K, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol* 2020; 38: 4138-48.

[16] Sun J-M, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *The Lancet* 2021; 398: 759-71.

[17] Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced Esophageal squamous-cell carcinoma. *N Engl J Med* 2022; 386: 449-62.

[18] Luo H, Lu J, Bai Y, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA* 2021; 326: 916-25.

[19] Lu Z, Wang J, Shu Y, et al. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. *BMJ* 2022; 377: e068714.

[20] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; 39: 1-10.

[21] Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. *Nat Rev Immunol* 2018; 18:153-67.

[22] Galluzzi L, Kepp O, Kroemer G. Immunogenic cell death in radiation therapy. *Oncoimmunology* 2013; 2: e26536.

[23] Arina A, Gutiontov SI, Weichselbaum RR. Ra-

diotherapy and immunotherapy for cancer: from "systemic" to "multisite". *Clin Cancer Res* 2020; 26: 2777-82.

[24] Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* 2015; 1: 1325-32.

[25] van Gulijk M, Dammeijer F, Aerts J, Vroman H. Combination strategies to optimize efficacy of dendritic cell-based immunotherapy. *Front Immunol* 2018; 9: 2759.

[26] Lugade AA, Sorensen EW, Gerber SA, Moran JP, Frelinger JG, Lord EM. Radiation-induced IFN-gamma production within the tumor microenvironment influences antitumor immunity. *J Immunol* 2008; 180: 3132-9.

[27] Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 2014; 124: 687-95.

[28] Yang H, Jin T, Li M, Xue J, Lu B. Synergistic effect of immunotherapy and radiotherapy in non-small cell lung cancer: current clinical trials and prospective challenges. *Precision Clinical Medicine* 2019; 2: 57-70.

[29] Salas Benito D, Perez-Gracia JL, Ponz-Sarvise M, et al. Paradigms on immunotherapy combinations with chemotherapy. *Cancer Discov* 2021; 11: 1353-67.

[30] Zhang W, Yan C, Zhang T, Chen X, Dong J, Zhao J, et al. Addition of camrelizumab to docetaxel, cisplatin, and radiation therapy in patients with locally advanced esophageal squamous cell carcinoma: a phase 1b study. *Oncoimmunology* 2021; 10: 1971418.

[31] Xi M, Zhu Y, Li Q, et al. The efficacy and safety of toripalimab combined with definitive chemoradiotherapy for patients with locally advanced esophageal squamous cell carcinoma. *J Clin Oncol* 2021; 39: e16043.

[32] Immune checkpoint therapy with nivolumab esophageal squamous cell carcinoma. Available from: https://ClinicalTrials. gov / show / NCT03278626.

[33] A study of toripalimab combined with concurrent chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. Available from: https://ClinicalTrials. gov / show/ NCT04084158.

[34] Shah MA, Kojima T, Hochhauser D, et al. Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. *JAMA Oncol* 2019; 5: 546-50.

[35] Wang F, Ren C, Zhao Q, et al. Association of frequent amplification of chromosome 11q13 in esophageal squamous cell cancer with clinical benefit to immune check point blockade. *J Clin Oncol* 2019; 37: 4036.

[36] Fei Z, Xie R, Chen Z, et al. Establishment of a novel risk score system of immune genes associated with prognosis in esophageal carcinoma. *Front Oncol* 2021; 11: 625271.

[37] Wang X, Zhang B, Chen X, et al. Lactate dehydrogenase and baseline markers associated with clinical outcomes of advanced esophageal squamous cell carcinoma patients treated with camrelizumab (SHR-1210), a novel anti-PD-1 antibody. *Thorac Cancer* 2019; 10: 1395-401.

[38] Zhu Y, Yao W, Xu BC, et al. Predicting response to immunotherapy plus chemotherapy in patients with esophageal squamous cell carcinoma using non-invasive Radiomic biomarkers. *BMC Cancer* 2021; 21: 1167.